Direct Synthesis of Amides from Carboxylic Acids and Amines by Using Heterogeneous Catalysts: Evidence of Surface Carboxylates as Activated Electrophilic Species

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Direct synthesis of amides from carboxylic acids and amines using heterogeneous catalysts: evidence of surface carboxylates as activated electrophilic species

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"Rethinking amide bond synthesis"[1] is one of the most stimulating topics in current chemical research. A number of successful amide-forming reactions have been proposed to meet highly demanding synthetic challenges and/or large-scale production requirements.[1] However, a general problem affecting these methods is the consumption of large amounts of chemicals, which typically include reagents required for the activation of carboxylic groups, resulting in increased costs and waste production. In 2007 the American Chemical Society Green Chemistry voted "amide bond formation avoiding poor atom economy reagents" as a top priority in the search for better and greener reagents and methods.[2] Catalyzed reactions are quite attractive for this purpose, and many compelling studies of amidation reaction promoted by homogeneous[3-6] and heterogeneous catalysts have been reported in recent years.[7-13] The amidation mechanism for unactivated carboxylic acids and amines on heterogeneous catalysts, in particular the activation of the carboxylic moiety, has not been sufficiently explored yet. Rimola et al. proposed a mechanism involving undissociated carboxylic groups for the formation of peptide bonds on the surface of an aluminosilicate, in their assessment of Bernal's hypothesis using ab initio methods.[14]

Herein, IR spectroscopy and high-resolution mass spectrometry (HR-MS) provide evidence of amidation under mild temperature conditions (ca. 323 K, the temperature of the samples in the IR beam, hereafter beam temperature, b.t.) from carboxylate moieties, formed by the adsorption of formic and acetic acids on the surface of TiO_2 nanoparticles (Degussa P25). In our view, this finding represents the starting point for the elucidation of the structural and energetic features of one of the potential pathways for amidation on surfaces, promoting the rational design of optimized materials and processes for heterogeneous catalytic approaches.

Formic acid was properly dosed from the vapor phase on dehydrated TiO_2 nanoparticles (experimental details in the Supporting Information – SI –, section Materials and Methods and Figure S1) in order to obtain only formate species adsorbed on the surface. The attainment of this target was witnessed by the selective appearance in the IR spectrum of components at 1560 cm^{-1}, with shoulders at 1580 and 1540 cm^{-1}, and at 1361 cm^{-1}, with a weak partner at 1412 cm^{-1}, due to the $\nu_{asym}COO^-$ and $\nu_{sym}COO^-$ of formate species, respectively, while the signal at 1385 cm^{-1} corresponds to the H-C-O bending mode[15-17] (Figure 1, curves a, b; spectra in the full range in Figures S1B and S2 in the SI). The same pattern was obtained using HCOOD molecules, thus confirming the selective formation of $HCOO^-$ species (Figure S1B' in the SI).

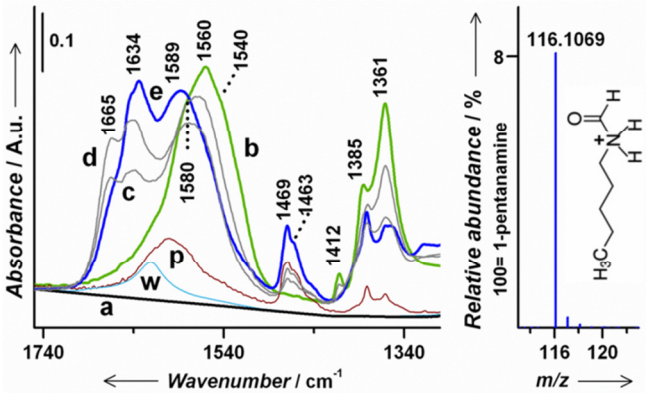

Figure 1. Left Panel. IR spectra, in the 1750-1300 cm^{-1} range, of TiO_2: (a) outgassed at 723 K; (b) after contact with HCOOH and subsequent outgassing; (c-e) after admission of increasing doses of 1-pentanamine; (p-w) curve **p** and curve **w** are the spectra of TiO_2 outgassed at 723 K, contacted with 40 mbar of 1-**p**entanamine and 20 mbar **w**ater vapors, respectively, and outgassed at b.t. for 1 h. Right panel: HR mass spectrum of the washing solution of the reacted sample. The original spectrum is in Figure S3A in the SI.

The higher coverage resulted in the appearance of the νC=O band at ca. 1682 cm^{-1}, which corresponds to HCOOH molecules adsorbed in the non-dissociated form (Figure S1A in the SI). A proposal of the formate coordination modes to surface cations, based on the splitting between the signals due to $\nu_{asym}COO^-$ and $\nu_{sym}COO^-$ bands ($\Delta\nu_{asym\text{-}sym}$), [17] is reported in Table S1A in the SI. Basically, at least two types of bridging formates, likely adsorbed on sites with different local structures, and one type of bidentate formate should be present.

Increasing amounts of 1-pentanamine vapors (this molecule was selected as the simplest aliphatic amine commercially available in a pure liquid form) were then added to the IR cell (Figure 1, curves c-e; spectra in the full range in Figure S2 in the SI) with the consequent consumption of the $\nu_{sym}COO^-$ signals at 1361 and 1412 cm^{-1} and of the $\nu_{asym}COO^-$ components at 1560 and 1540 cm^{-1} occurred, as well as an appearance of two bands at 1665 and 1634 cm^{-1}. At the end of the process, the signal at 1665 cm^{-1} decreased in intensity, appearing as an ill resolved shoulder of the band at 1634 cm^{-1} (Figure 1, curve e). The component at lower frequency became more intense and broader, with an up-shift of the maximum from 1580 to 1589 cm^{-1}, likely because of the growth of a subband due to the δNH_2 mode (Figure 1, curve p). The new absorptions at 1665 and 1634 cm^{-1} appeared located in a spectral region where νC=O signals due to amide species occur.[18a-19]

As for the δC-N-H + νC-N band (amide II) typical of amides, it could contribute to the low frequency tail of the band with maximum at 1589 cm^{-1}.[18a-20] The occurrence of amidation reaction was confirmed by the high resolution mass spectrum (see SI, Methods and Figure S3A) of the aqueous solution resulting from the washing of the sample (extraction yield ≈ 90%; Figure S4 in the SI), which exhibited the signal at m/z = 116.1069 due to protonated N-pentylformamide (Figure 1, right panel). One of the other expected products of amidation, H_2O molecules (see Chart 1), should contribute to the pattern in the 1700-1500 cm^{-1} region with the δH_2O signal. Indeed, curve w in Figure 1 is the δH_2O band of water molecules left adsorbed after outgassing at b.t. on a TiO_2 sample with a "similar optical density" (mg/cm^2), and represents the maximum amount of H_2O molecules that can be retained on the catalyst surface. Focusing on the occurrence of the amidation reaction, the interaction of the carboxylate oxygen atoms with surface Ti^{4+} ions, acting as Lewis acid centres, is expected to withdraw electron density from the C atom, which becomes electrophilic enough to undergo nucleophilic attack by the nitrogen atom of the amine. The consistency of the $\nu_{asym}COO^-$ component at 1580 cm^{-1} (with a weaker $\nu_{sym}COO^-$ partner in the 1370-1350 cm^{-1} region), related to one type of bridging formate, indicated that such activation is dependent on the structure of the carboxylate-surface complex, even within the same coordination mode to the surface.

A schematic drawing of main molecular events occurring at the surface is depicted in Chart 1.

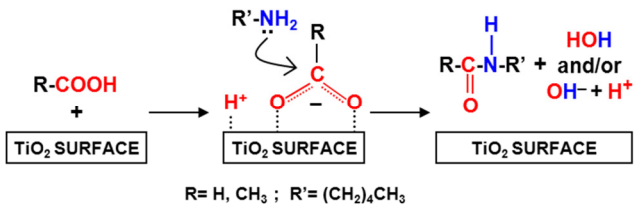

Chart 1. Scheme of the amidation reaction involving surface carboxylates.

The current data do not allow us to establish whether the carboxylate reacts with pentanamine in the gas phase and/or both species are adsorbed on the surface, as well as hydroxy groups and/or water molecules are formed. The presence of two νC=O signals attributed to amide species was the object of further investigation. The decrease of the 1665 cm^{-1} component at the end of the process (Figure 1, curve e) was partly reversed by subsequent outgassing (Figure S5A in the SI).

This band was also present in the spectrum of the sample hydrated by contact with H_2O vapor and then outgassed at b.t. (Figure S5B in the SI), whereas it disappeared when D_2O was used (Figure S5C in the SI). The explanation of a such complex behaviour is outside the scope of this contribution, but the overall data suggest that an interplay between the interaction of amide species with the surface (favored at low amides content), water molecules produced during the reaction, and vibrational coupling involving C=O and H_2O, not occurring with D_2O,[19] should be taken into account.

As for the amidation reaction, essentially the same final spectral pattern was obtained by reversing the order of the admission of the reactant on the TiO_2 surface (Figure S6 in the SI). Unfortunately, the reaction proceeded too quickly to monitor the non-dissociative adsorption of HCOOH molecules. Therefore, on one hand the potential activation of the non-dissociated formic acid molecules could not be investigated, and, on the other hand a pathway that involves HCOOH molecules undergoing deprotonation by interaction with free surface sites, cannot be excluded.

Another crucial point is the type of surface sites involved in the formation of formate. The disappearance of the original νOH pattern of TiO_2 (Figure S1 in the SI) indicated that surface hydroxy groups are involved in the formation of formates. These groups represent a small fraction of surface sites on TiO_2 P25 particles outgassed at 723 K, which overwhelmingly expose Ti^{4+} and O^{2-} sites.[21] IR spectroscopy of adsorbed CO was employed to probe the exposure of cationic centers before and after the formation of $HCOO^-$ species. The results revealed that the formate species occupied a significant portion of the surface of TiO_2 particles (Figure S7 in the SI), which primarily expose (101) facets,[21] where HCOOH and CH_3COOH have been proposed to be adsorbed dissociatively,[15, 22] as well as on (001) facets[23] that represent a minor fraction of TiO_2 P25 surface terminations.[21]

Similar experiments using acetic acid demonstrated the effectiveness of surface activation also towards a carboxylic acid with a substituent exhibiting a +I inductive effect (CH_3COOH pK_a 4.76; HCOOH, pKa 3.75). [24] The spectral pattern exibited bands in the 1650-1350 cm^{-1} region, due to $\nu_{asym}COO^-$ and $\nu_{sym}COO^-$ bands (Figure 2, curves a,b), monitoring the formation of acetate species (spectra in the full range in Figure S8 in the SI). The νC=O signal in the 1690-1670 cm^{-1} range, typical of non-dissociated CH_3COOH was absent, whereas it appeared at higher coverage (Figure S9 in the SI). It was difficult to distinguish subbands in the $\nu_{asym}COO^-$ signal at 1533 cm^{-1}, while the $\nu_{asym}COO^-$ band resulted from the superposition of at least two components, at 1454 and 1410 cm^{-1}, in addition to a shoulder at ca. 1470 cm^{-1}, containing a contribution of the δCH_3 mode.[17-18b] The structures of adsorbed acetate species, mainly of the bidentate type, are summarized in Table S1B in the SI.

The subsequent addition of 1-pentanamine resulted in a complex evolution of these signals with the appearance of a new banding pattern containing a shoulder at ca. 1633 cm^{-1}, which became more resolved after outgassing at room temperature (Figure 2, curve d'). This component is attributed to the νC=O mode of the newly formed amide species.[18a-19]

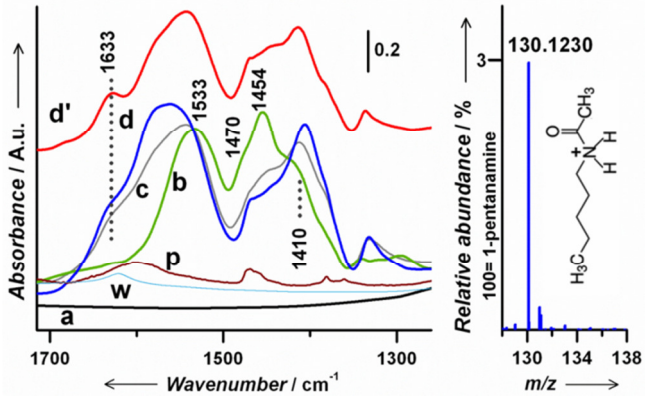

Figure 2. Left panel. IR spectra, in the 1715-1260 cm^{-1} range, of: (a) TiO_2 outgassed at 723 K; (b) after contact with CH_3COOH and subsequent outgassing (details in the SI, Figure S7B); (c-d) after admission of increasing doses of 1-pentanamine; (d') spectrum collected after outgassing at b.t. for 1 h at the end of the reaction; curves p and w, reported for the sake of completeness, are as in Figure 1. Right panel: portion of HR mass spectrum of the washing solution of the reacted sample, showing the m/z signal of protonated N-pentylacetamide. The original spectrum is in Figure S3B in the SI.

The HR-MS analysis of the aqueous washing solutions (extraction yield of ca. 90%, see Figure S3 in the SI) confirmed this result (Figure 2, right panel, signal at m/z = 130.1230 due to protonated N-pentylacetamide).

Back to the IR data, the remaining modifications in the spectral pattern in Figure 2 can be attributed to non-reactive adsorbate-adsorbate interactions among amine molecules and acetates, because of the similar evolution of the spectrum observed upon the D_2O addition (which does not interfere with other IR signals in the 1700-1300 cm^{-1} range) on the pre-adsorbed acetates (Figure S10 in the SI).

The potential of carboxylic acids to be activated for amidation on the surface of an oxide through the formation of carboxylates has been demonstrated. Such a mechanism could be proposed as the basis for the catalytic activity in amidation exhibited by TiO_2 [12-13] and other partly ionic or almost fully ionic oxides, such as ZnO [7] and MgO,[9] respectively. Specific studies will follow for other materials that exhibit effective catalytic activity for amidation, such as covalent oxides like silica, where the activating sites have been proposed to be strained siloxane bridges,[8] or salts.[10]

Experimental Section

Descriptions of materials, of IR and HR-MS methods, and additional results [IR spectra of: increasing/decreasing amount of HCOOH on TiO_2; HCOOH and 1-pentanamine adsorption on TiO_2; washed samples; reacted sample outgassed and hydrated with H_2O or D_2O; reverse order of admission of HCOOH and 1-pentanamine on TiO_2; adsorbed CO; CH_3COOH and 1-pentanamine adsorption on TiO_2; increasing/decreasing amount of CH_3COOH on TiO_2; D_2O admitted on CH_3COO^-/TiO_2; summary of the structures of surface carboxylates; HR-MS spectra] are reported in the Supporting Information.

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Keywords: Amide bond synthesis • metal oxide catalysis • surface carboxylate activation

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